# Metformin or Oral Contraceptives for Adolescents With Polycystic Ovarian Syndrome: A Meta-analysis

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abstract

**BACKGROUND:** Polycystic ovarian syndrome (PCOS) is a common disease. There is limited evidence to support various treatment choices. This leads to variable treatment practices.

**OBJECTIVES:** To conduct a systematic review and meta-analysis of randomized controlled trials (RCTs) to evaluate the use of metformin versus oral contraceptive pills (OCPs) for the treatment of PCOS in adolescents aged 11 to 19 years.

**DATA SOURCES:** We performed literature searches through Ovid Medline, Ovid Embase, Cochrane Central Register of Controlled Trials, and gray literature resources, up to January 29, 2015.

**STUDY SELECTION AND DATA EXTRACTION:** Two reviewers screened titles and abstracts of identified citations, assessed full text eligibility, and extracted information from eligible trials.

**RESULTS:** Four RCTs met the inclusion and exclusion criteria. The reviewed evidence came from 170 patients. Overall, OCP treatment resulted in modest improvement in menstrual cycle frequency (weighted mean difference [WMD] = 0.27, $P < .01$, 95% confidence interval [CI] −0.33 to −0.21) and mild reduction of acne scores (WMD = 0.3, $P = .02$, 95% CI 0.05 to 0.55). While metformin resulted in greater BMI reduction (WMD = −4.02, $P < .01$, 95% CI −5.23 to −2.81) it was associated with decreased dysglycemia prevalence (risk ratio: 0.41, $P = .02$, 95% CI 0.19 to 0.86) and improved total cholesterol and low-density lipoprotein levels. Metformin and OCPs were similar in terms of impact on hirsutism.

**CONCLUSIONS AND LIMITATIONS:** Current evidence is derived from very low to low quality evidence. Therefore, treatment choice should be guided by patient values and preferences while balancing potential side effects. Future high quality RCTs are needed to address several questions for the treatment of adolescents with PCOS.

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Polycystic ovarian syndrome (PCOS) is a common reproductive endocrine disease that is encountered in adolescence. The prevalence of PCOS varies between 1.8% and 15% depending on ethnic background and the diagnostic criteria used.[1–3] PCOS presents with a constellation of symptoms including chronic anovulation (amenorrhea, oligomenorrhea, and irregular menstrual cycles), clinical features of hyperandrogenism (acne and hirsutism), biochemical hyperandrogenism, polycystic ovaries on ultrasound, and features of metabolic syndrome.[4] The etiology of PCOS is not well understood; primary intrinsic ovarian pathology along with hypothalamic–pituitary–ovarian axis abnormalities may lead to increased ovarian androgen secretion.[5,6] Also, a primary metabolic abnormality theory suggests that insulin resistance with compensatory hyperinsulinemia is the primary cause of PCOS features.[5–8]

Insulin resistance plays a major role in the development of the cardiometabolic disturbances associated with PCOS such as dysglycemia, hyperlipidemia, and obesity.[9–11] In adolescents with PCOS, 18% to 24% have abnormal glucose metabolism (3% to 4% impaired fasting glucose, 13% to 15.2% impaired glucose tolerance, and 1.5% type 2 diabetes [T2DM][12–14]). These metabolic disturbances are associated with an increased prevalence of T2DM, myocardial infarction, infertility, gestational diabetes, premature delivery, and risk for gynecologic cancers.[15–20] In addition, patients report low perceived health-related quality of life due to the symptoms of PCOS, particularly related to obesity, hirsutism, acne, and menstrual irregularity.[21–23]

The Endocrine Society guidelines for the treatment of adults with PCOS recommends using oral contraceptive pills (OCPs) to control symptoms of hyperandrogenism and to provide contraception when pregnancy is not desired, while reserving metformin for cases with impaired glucose tolerance or features of metabolic syndrome.[4] However, there is lack of evidence to support the best first-line medication in adolescents with PCOS after initial lifestyle interventions have been tried. PCOS treatment presents clinical equipoise that is highlighted by the lack of consensus between guidelines around the world for the best treatment approach.[24–26] Therefore, we aimed to evaluate the effectiveness of metformin use versus OCP in adolescents aged 11 to 19 years with PCOS in improving menstrual cyclicity, clinical hyperandrogenism, and metabolic profile.

## METHODS

The following methodological description was proposed in an a priori fashion with a registered protocol with PROSPERO (CRD42015020922). In creating the report of this systematic review, we followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement.[27]

### Inclusion and Exclusion Criteria

The search for studies was limited to randomized controlled trials (RCTs) that evaluated adolescents aged 11 to 19 years with PCOS. The age limits were based on the World Health Organization definition of adolescence.[28] The diagnosis of PCOS was based on any of the known PCOS diagnostic criteria: Endocrine Society Guidelines, the Rotterdam criteria, National Institutes of Health (NIH), and the Androgen Excess Society criteria.[4,29,30] Subjects with other causes of oligomenorrhea or hyperandrogenism, such as hyperprolactinemia, thyroid dysfunction, androgen secreting tumors, or late-onset congenital adrenal hyperplasia were excluded.

The included studies evaluated the effectiveness of any dose of metformin versus any type of OCP. We included studies that used add-on therapy (cointervention) with pioglitazone, spironolactone, flutamide, or lifestyle interventions for treating PCOS. Included studies must have revealed the effectiveness of 1 of the previous interventions with 1 or more outcome(s) of interest. We excluded studies that used fertility induction medications for pregnancy as a primary interest. Substudies of reported eligible studies were excluded to avoid duplication.

### Outcomes Measures

The primary outcomes were menstrual regulation (cycle/month) and hirsutism scores (Ferriman Gallwey score). Secondary outcomes included acne scores (Cook's numeric grading), prevalence of dysglycemia (number of participants diagnosed with T2DM and/or prediabetes), BMI, total testosterone level (nmol/L), and lipid profile as a surrogate marker for cardiovascular disease (triglyceride, total cholesterol, low-density lipoprotein [LDL], and high-density lipoprotein [HDL]; mg/dL). We included dysglycemia as a composite outcome to answer the growing clinical concern that OCPs lead to disturbances in glucose metabolism and increased risk of prediabetes and T2DM in a population that already has an increased baseline risk for prediabetes and T2DM.[12–14,31]

## DATA COLLECTION, SYNTHESIS, AND ANALYSIS

### Data Sources and Search Strategy

We performed literature searches through Ovid Medline (1946 to January 29, 2015), Ovid Embase (1974 to January 27, 2015), and Cochrane Central Register of Controlled Trials (January 30, 2015).

The search terms used included combinations of subject headings and keywords with various synonyms for PCOS, adolescent, metformin, pioglitazone, OCP, flutamide, and lifestyle interventions (Supplemental Information). We used the RCT filter created from McMaster University for Ovid Embase platform, and the Cochrane library filter for Ovid Medline platform.[32,33] These filters provide a good balance between sensitivity and specificity for the identification of RCTs. We developed our search strategy in liaison with an experienced academic librarian. No language, publication status, or date limits were set. We performed gray literature searches by using multiple resources (Supplemental Information). We contacted authors of unpublished work to establish eligibility and methodological quality of the studies. Search alerts were set up for monthly notification, and the search was repeated before the production of the final article to identify any new literature.

### Selection of Studies

One of the authors (Dr Al Khalifah) performed the search for primary studies. Two reviewers (Drs Al Khalifah and Florez) independently screened titles and abstracts retrieved to assess the study's eligibility. In case of disagreement, the full text was retrieved and reviewed independently by 2 of the reviewers (Drs Al Khalifah and Bassilious). We referred to the inclusion and exclusion criteria during the screening process. Records of ineligible studies along with the reason for ineligibility were saved for future reference. Eligible studies citations were saved in an EndnoteX6 library file.

### Data Extraction

An online form (Google forms) was used for data extraction according to standardized prespecified instructions. All reviewers independently piloted the data extraction form. Additionally, to establish calibration, all reviewers completed data extraction on 2 full studies. Three reviewers (Drs Al Khalifah, Florez, and Dennis) performed data extraction and methodological quality assessment for each study independently in pairs. In case of disagreement, it was resolved by discussion and consensus, and referred to the third reviewer to resolve any disagreement if consensus was not reached. Reviewers contacted the authors of primary studies to provide any missing information or clarification. As a result, some unpublished data were included in the analysis.

### Assessment of Risk of Bias and Quality of the Evidence in Included Studies

Two independent reviewers (Drs Al Khalifah, Florez, and Dennis) assessed each study for risk of bias by using a modification of the Cochrane handbook for systematic reviews.[34,35] The tool evaluates 6 elements in each study: the sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, completeness of follow up, selective outcome reporting, and presence of other biases. Each domain was assigned a score: "low risk," or "high risk" or "unclear risk." However, we further categorized the unclear risk to "probably low risk," or "probably high risk." These 2 categories were used to aid the reviewer in assigning either low risk or high risk to the study and to give a better understanding of the unclear risk of bias score.[36] We rated the overall risk of bias score for each study as high risk if the study met more than 2 criteria for high risk of bias, "moderate risk of bias" if the study met 1 to 2 criteria for high risk of bias, and "low risk of bias" if the study did not meet any high risk of bias criteria.

The quality of the evidence for each reported outcome was assessed independently by (Drs Al Khalifah and Florez) using the Grading of Recommendations Assessment, Development, and Evaluation Working Group (GRADE) approach.[37] The GRADE approach is based on the assessment of 5 elements: (1) risk of bias, (2) imprecision, (3) inconsistency, (4) indirectness, and (5) publication bias.[38]

### Statistical Analysis

Statistical analyses were performed in accordance with the guidelines for statistical analysis developed by The Cochrane Collaboration.[33] The analyses were performed by using the Cochrane Collaboration Review Manager Version (RevMan 5.2). The online GRADE-Pro-Guidelines Development Tool was used to produce the summary of finding table, and GRADE tables.

Effect estimates are presented as weighted mean differences (WMDs) and 95% confidence interval (CI) SDs for continuous data, and risk ratio (RR) with 95% CI for dichotomous data. Data were pooled by using the fixed-effect model. Heterogeneity was assessed for each outcome by using the Cochran's Q statistic and quantified by the $I^2$ score. We interpreted the $I^2$ by using the thresholds suggested by the Cochrane Collaboration.[33] An $I^2$ >50% indicated the presence of at least moderate heterogeneity, and in this case we used the random-effect model to pool the effect estimates if heterogeneity could not be explained by subgroup analysis. A priori we decided to perform subgroup analysis provided there was a minimum of 2 studies in 1 subgroup to safeguard against spurious subgroup findings. Otherwise the quality of evidence was downgraded for that specific outcome. A priori we hypothesized that differences in ethnic background, medication dose,

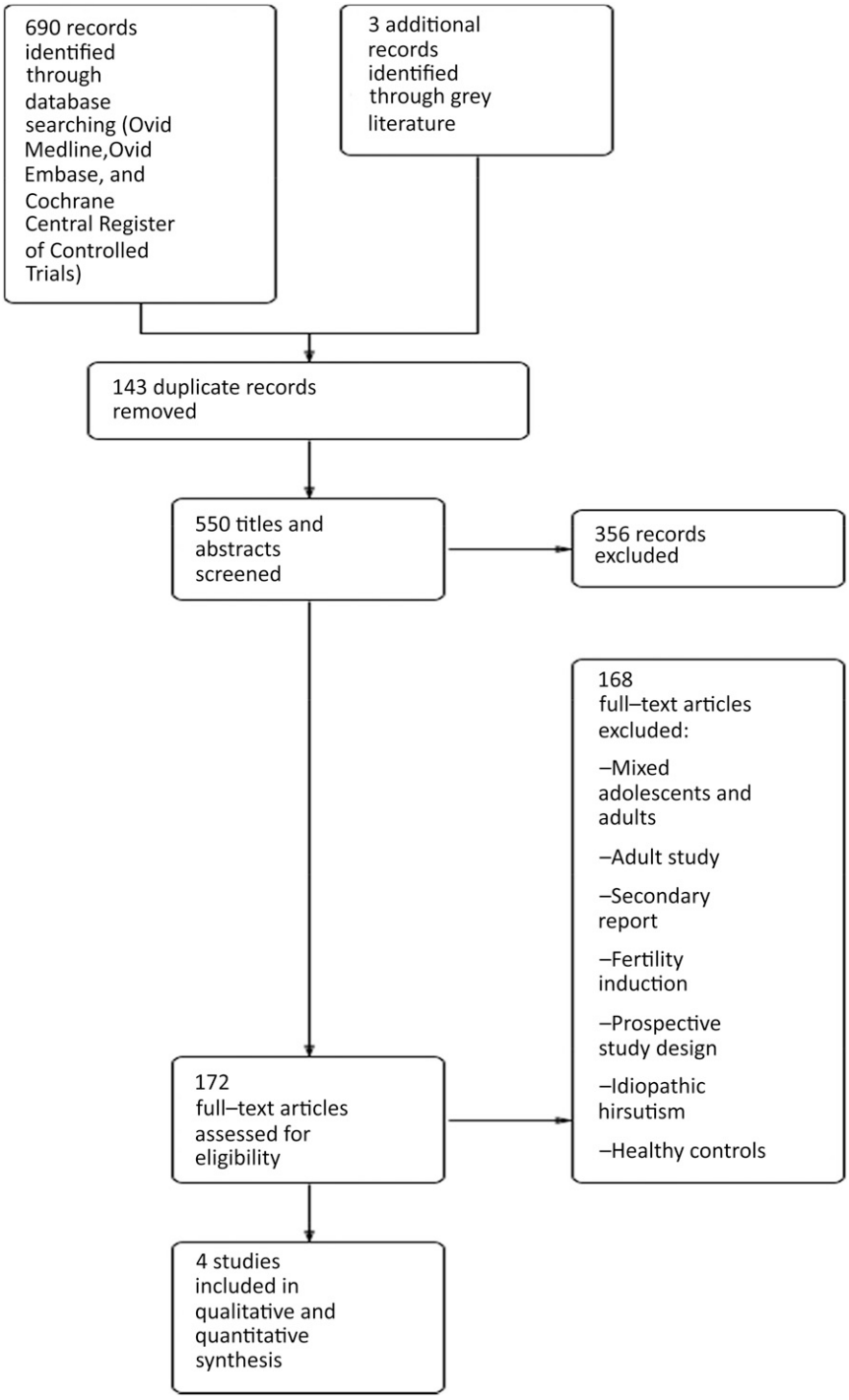


**FIGURE 1**
Study flow diagram.

treatment duration (≤6 months versus >6 months), use of ultrasound to document polycystic ovaries (used versus not used), and cointervention with other medications (pioglitazone, spironolactone, flutamide, lifestyle interventions) would explain observed heterogeneity in our results. Finally, we planned to perform a formal assessment of the risk of publication bias by constructing funnel plots. However, there was not a sufficient number of studies to develop these graphs.

## RESULTS

### Search for Studies

Our literature search identified 693 potentially relevant references. After removal of the 143 duplicates, a total of 550 references were screened by title and abstracts. After screening, 172 studies were identified as potentially eligible. Subsequently, the full texts of the 172 studies were reviewed revealing 4 studies, which met inclusion and exclusion criteria, and 42 studies that had included adults and adolescents or used multiple combinations of pioglitazone, spironolactone, or flutamide in addition to metformin and OCP. The excluded studies along with reasons for exclusion are included in the Supplemental Information. Study flow diagram is shown in Fig 1.

### Study Characteristics

Four RCTs were included.[39–42] Table 1 reveals the summary of all included studies, Table 2 reveals baseline characteristics for all outcomes, and Supplemental Tables 7, 8, 9, and 10 reveal a detailed summary of each study. All studies used the NIH criteria to diagnose PCOS. Additional inclusion criteria identified were obesity (all studies) and hyperinsulinism.[39] All studies excluded non-PCOS causes of hyperandrogenism (adrenal cancer, congenital adrenal hyperplasia, ovarian cancer, and hyperprolactinemia), liver or kidney disease. Three studies excluded current or recent use of metformin or OCP.[40–42] None of the studies described the specific ethnic origin of the participants per intervention arm.

In 1 study,[41] participants received routine counseling about diet and exercise but no specific exercise or diet prescription was offered. The total number of patients in these studies was 231 patients; 170 were randomly assigned to receive

**TABLE 1** Summary of the Included Trials

| Study | Location | Total Trial Patients, *N* | Included in the Systematic Review, *N* | Lost to Follow-Up, *N* | Age, y | Duration, mo | Metformin Dose | OCP Type and Dose | Outcomes |
|---|---|---|---|---|---|---|---|---|---|
| Al-Zubeidi 2015 | United States | 34 | 34 | 12 | 14–18 | 6 | 1000 BID | Norethindrone1 mg, ethinyl estradiol 30 μg | Hirsutism<br>BMI<br>Lipid profile<br>Total testosterone<br>Side effects |
| Allen 2005 | United States | 35 | 35 | 4 | 12–21 | 6 | 1000 BID | Norgestimate 0.25 mg, ethinyl estradiol 35 μg | Menstrual regulation<br>Hirsutism<br>Acne<br>BMI<br>Lipid profile<br>Total testosterone |
| Hoeger 2008 | United States | 43 | 21 | 5 | 12–18 | 6 | 850 BID | Desogestrel 0.15 mg, ethinyl estradiol 30 μg | Menstrual regulation<br>Hirsutism<br>Dysglycemia<br>BMI<br>Lipid profile<br>Total testosterone |
| El Maghraby 2014 | Egypt | 119 | 80 | 15 | 15–20 | 24 | 850 BID | Progestin 15 mg, ethinyl estradiol 30 μg | Menstrual regulation<br>Hirsutism<br>BMI<br>Lipid profile<br>Total testosterone<br>Side effects |
| Total | | 231 | 170 | 36 | | | | | |

BID, 2 times daily.

metformin or OCP, and 36 were lost to follow-up because of various causes (loss of interest, treatment side effects, lack of improvement, or moving away).

## Risk of Bias in Included Studies

All the studies were judged to be at low risk of bias for randomization. Concealment of allocation was judged to be at low risk of bias for 2 studies[39,42] in which treatment was allocated through sealed envelopes. The other 2 studies were judged to be at high risk of bias. Concealment of allocation was not disclosed in 1 study[41] and another study[40] revealed semiopen concealment (eg, the metformin and placebo groups were concealed but OCP and lifestyle intervention groups were not concealed). All studies were unblinded except for 1 study[40] where participants in the metformin and placebo groups were blinded, but participants in the OCP and lifestyle intervention arms were not blinded.

Three studies performed complete case analyses (only participants who completed the study were included), and 1 study that performed intention-to-treat analysis (all participants were included in the analysis because there were no patient withdrawals).[42] Three studies[40–42] were judged to be at high risk of bias for loss of follow-up (loss to follow-up rate >20% for some treatment arms). Additionally, selective reporting was suspected in 1 study[41] and was therefore rated as high risk of bias because of a large discrepancy between the published abstract and the final study report.[43] Figure 2 reveals summary of risk of bias assessments.

## Effects of the Interventions

### *Menstrual Regulation*

Two studies compared metformin versus OCP.[39,40] They reported menses as the mean number of menstrual cycles per month[39] and per every 3 months.[40] One study[39]

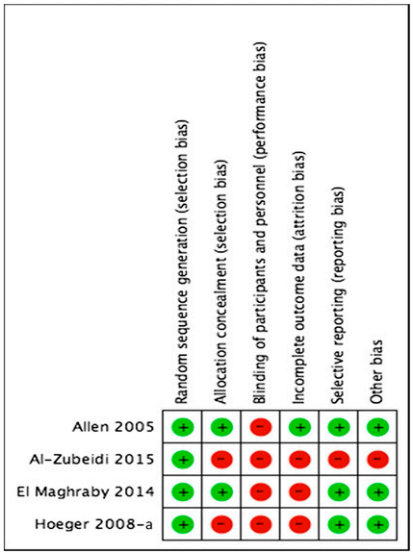


**FIGURE 2**
Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies

revealed a statistically significant difference between groups favoring OCP (WMD −0.15, 95% CI −0.22 to −0.08), whereas the other study revealed menstrual regulation for the metformin group only (mean ± SD = 0.5 ± 0.1).[40] We were unable to include the unavailable information for the OCP group. We performed a posthoc sensitivity analysis for the missing outcome data on the basis of a best case scenario (mean menstrual cycle of 1 cycle per month) and a worst case scenario (mean menstrual cycle of 0.75 cycle per month) as reported in the Allen et al[39] study for the OCP group. We also examined other plausible values on the basis of a 10% rate of amenorrhea and a menstrual cycle frequency of 2 per month (mean of 0.95), and a 20% rate of amenorrhea and a menstrual cycle frequency of 3 per month (mean of 0.86) as assumed from the literature on menstrual bleeding pattern in women taking OCP.[44–47] The SD was fixed for all the 4 analyses and assumed to be 0.1 as reported in the Allen et al[39] study and in the metformin group of the Hoeger et al[40] study. Figure 3 reveals all 4 analyses in the forest plots.

**TABLE 2** Baseline Outcome Measures

| | Metformin | OCP |
|---|---|---|
| Menstrual cycle, cycle/year | <8 | <8 |
| Hirsutism, F-G scale | 10.4 ± 5.1 | 12.1 ± 6.9 |
| Acne, Cook scale | 1.1 ± 0.4 | 2.1 ± 5.3 |
| BMI | 35.8 ± 6.1 | 36.8 ± 6.4 |
| Testosterone, nmol/L | 3.0 ± 0.9 | 2.9 ± 1.1 |
| Triglyceride, mg/dL | 125.8 ± 56.1 | 106.0 ± 33.8 |
| Total cholesterol, mg/dL | 162.3 ± 28.5 | 176.1 ± 36.9 |
| LDL, mg/dL | 103.9 ± 23.2 | 119.0 ± 24.1 |
| HDL, mg/dL | 43.0 ± 9.1 | 37.6 ± 7.5 |

All data are presented as mean ± SD. F-G scale, Ferriman-Gallwey Scale.

The estimate of the treatment effect favored OCP (best case WMD −0.27, $P < .01$, 95% CI −0.33 to −0.21; worst case WMD −0.19, $P < .01$, 95% CI −0.25 to −0.13). However, this point estimate represents a 1- to 2-week difference in the frequency of menstrual cycles per month, which is equivalent to 3.24 menstrual cycles per year. The heterogeneity examined by $I^2$ was 59% to 95%.

### *Hirsutism*

Three studies compared metformin versus OCP in terms of impact on hirsutism.[39,40,42] There was no statistically significant difference between groups (WMD 0.54, $P = .5$, 95% CI −1.23 to 2.31; Fig 4). There was moderate heterogeneity detected ($I^2 = 52\%$, $P = .12$) and therefore the estimate was pooled with random effects.

### *Acne Scores*

Only 1 study[39] revealed facial acne scores among 31 patients (35 randomly assigned patients). After intervention, there was a statistically significant difference between groups favoring OCP (WMD 0.3, $P = .02$, 95% CI 0.05 to 0.55). Heterogeneity assessment is not applicable for 1 study.

### *Dysglycemia*

Two studies[40,42] revealed dysglycemia among 81 patients. The diagnosis of T2DM or prediabetes was evaluated by oral glucose tolerance test (OGTT). The prevalence of dysglycemia at baseline was 25% to 35%. After intervention, there was a statistically significant difference between groups favoring Metformin over OCP (RR 0.27, $P = .01$, 95% CI 0.1 to 0.76), detected $I^2 = 0\%$ (Fig 5).

### *Body Mass Index*

All studies revealed BMI among 149 patients. After intervention, there was a statistically significant difference between groups favoring metformin over OCP (WMD −4.02, $P < .001$, 95% CI −5.23 to −2.81; Fig 6). There was significant heterogeneity detected $I^2 = 92\%$. This heterogeneity was explained with the a priori subgroup analysis on the basis of study duration. The test for subgroup differences was significant $\chi^2 = 36.36$, $df = 1$ ($P < .001$; Supplemental Fig 15). Supplemental Figs 12, 13, and 14 reveal the other subgroup analyses.

### *Total Testosterone*

All studies revealed total testosterone. After intervention, there was no statistically significant difference between groups (WMD 0.74, $P = .1$, 95% CI −0.22 to 1.70; Supplemental Fig 7).

## Lipid Profile

### *Triglyceride*

Three studies[39–41] revealed triglyceride levels. After intervention, there was no statistically significant difference between groups (WMD −9.69, $P = .4$, 95% CI −31.32 to 11.95; Supplemental Fig 8).

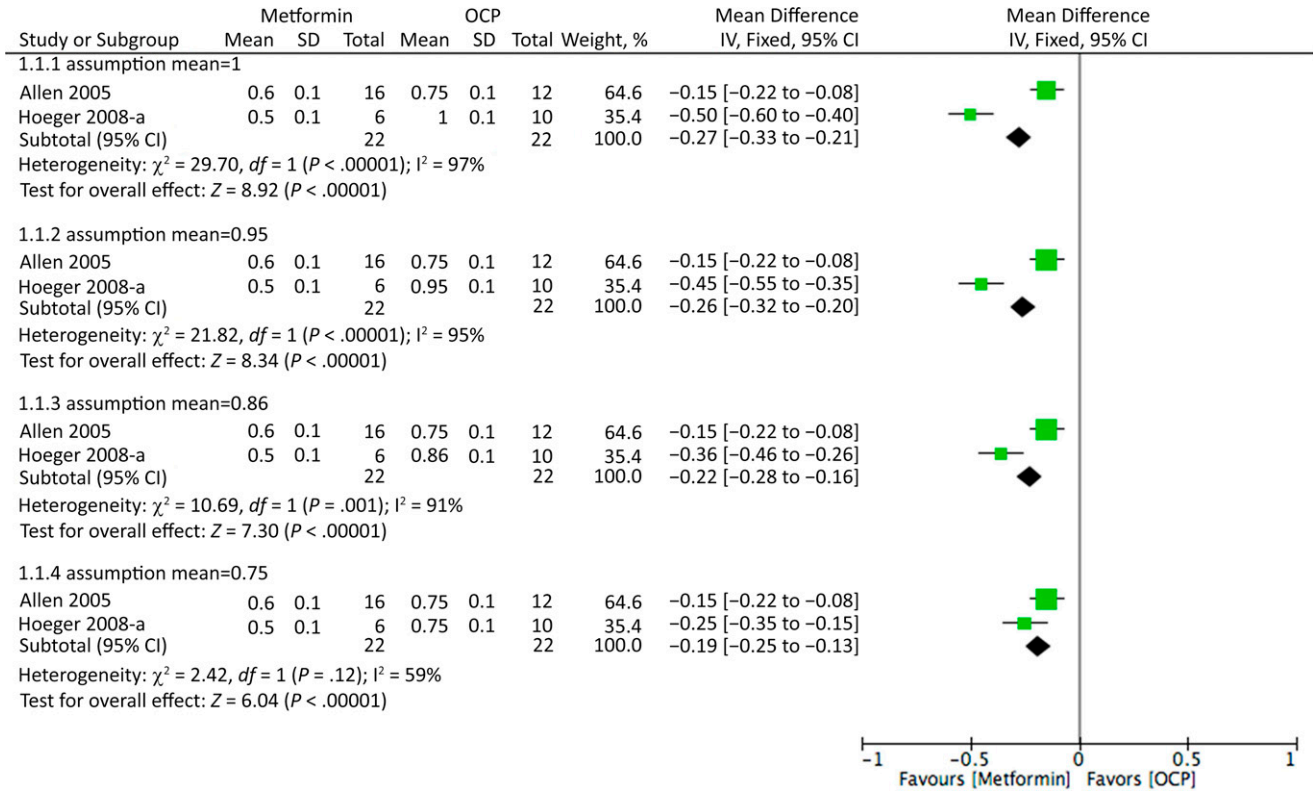


**FIGURE 3**
Forest plot of comparison: 1 metformin versus OCP, outcome: 1.1 menstrual cycle regulation sensitivity analyses.

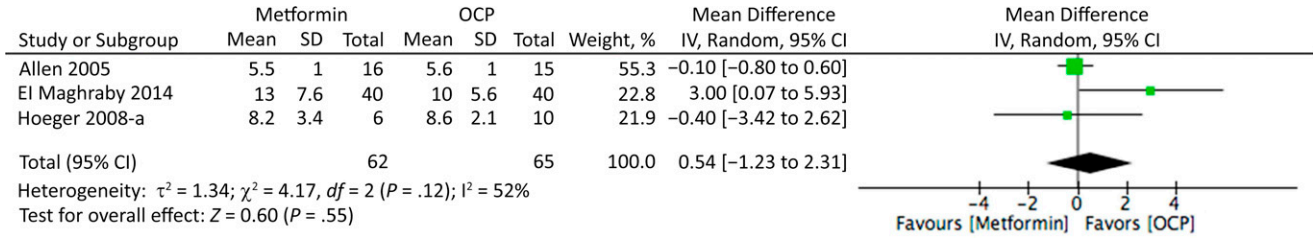


**FIGURE 4**
Forest plot of comparison: 1 metformin versus OCP, outcome: 1.2 hirsutism.

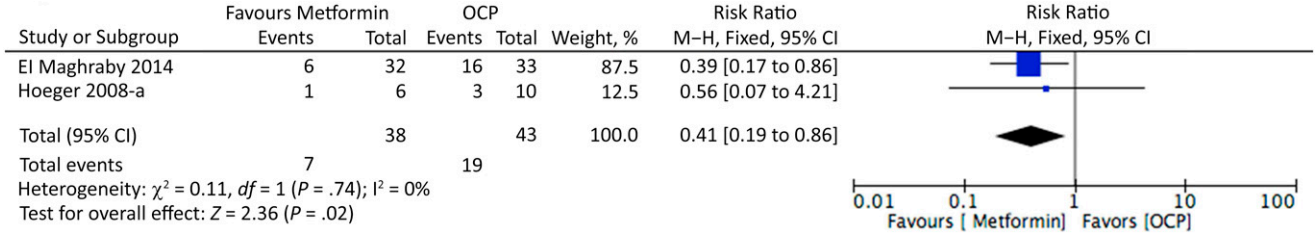


**FIGURE 5**
Forest plot of comparison: 1 metformin versus OCP, outcome: 1.5 dysglycemia.

### *Total Cholesterol*

Two studies[39,40] revealed total cholesterol. After intervention, there was a statistically significant difference between groups favoring metformin over OCP (WMD −43.23, $P < .001$, 95% CI −64.15 to −22.32; Supplemental Fig 9).

### *Low-Density Lipoprotein*

Two studies[39,40] revealed LDL. After intervention, there was a statistically significant difference between groups

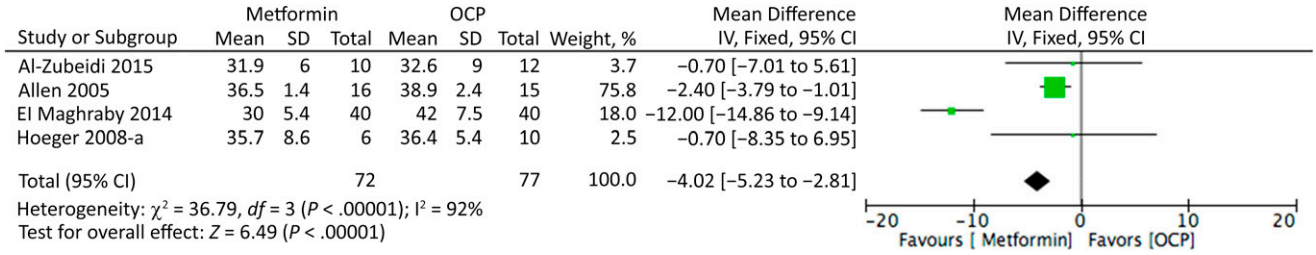


**FIGURE 6**
Forest plot of comparison: 1 metformin versus OCP, outcome: 1.4 BMI.

favoring metformin over OCP (WMD −35.50, $P = .002$, 95% CI −57.45 to −13.55; Supplemental Fig 10).

### *High-Density Lipoprotein*

Three studies[39–41] revealed HDL. After intervention, there was no statistically significant difference between groups favoring OCP over metformin (WMD 0.71, $P = .9$, 95% CI −12.42 to 13.83; Supplemental Fig 11).

### *Adverse Events*

Two of the authors supplemented adverse events when contacted.[41,42] The adverse events were variable and not consistently described and therefore impossible to pool. El Maghraby et al[42] reported mild gastrointestinal, headache, mastalgia, and mood change. Al-Zubeidi et al[41] reported nausea, stomach upset, and diarrhea in 30% of the patients enrolled in the metformin group, and no adverse events in the OCP group. These are summarized in Supplemental Table 11.

## Publication Bias

Although publication bias was highly suspected on the basis of finding 2 studies through gray literature searches, we had also identified many studies that included adolescents and adults. Therefore, we did not perform statistical testing for publication bias.

## Certainty of the Evidence

Overall the quality of evidence of the included studies was low (Table 3). The quality of evidence for all outcomes was downgraded by 2 levels for serious risk of bias at the study design level. Further downgrading per outcome was warranted because of imprecision resulting from small sample sizes and small event rates that did not reach the calculated optimal information size per outcome.

# DISCUSSION

Our search for studies of metformin versus OCP for the treatment of PCOS in adolescents yielded 4 studies that met our inclusion and exclusion criteria. The reviewed evidence was derived from a very small sample size (170 patients) with a maximum of 149 patients contributing results to 1 of the outcomes. The summary of findings for all outcome measures is shown in Table 3. Overall OCP treatment resulted in a modest improvement in menstrual cycle frequency by 0.27 cycle per month and mild reduction of acne scores by 0.3. Metformin resulted in a significant BMI reduction by 4.02 compared with OCP. Subgroup analysis for BMI on the basis of treatment duration suggested significant weight reduction with longer metformin use. However, this should be interpreted with caution because the analysis was derived from 4 small studies with a high risk of bias.[48] Metformin was associated with lower risk for dysglycemia (RR = 0.41) and improved total cholesterol and LDL levels. Both metformin and OCP had similar impacts on hirsutism scores, triglyceride, and HDL level.

This is the first systematic review and meta-analysis for the treatment of PCOS in adolescents comparing metformin versus OCP. To date, there is 1 published systematic review and meta-analysis for adults with PCOS that compared metformin to OCP.[49] This study pooled results from 6 studies, with 174 patients included in the analysis. All the included studies lacked blinding except for 1 study where the outcome assessors were blinded. This adult-focused systematic review revealed a similar effect estimate with wider CIs compared with our results.[49] Similar to our results, they reported higher menstrual bleeding (measured as proportion of women with regular menses). They did not, however, provide estimates in terms of mean number of menses per month. In their meta-analysis, there was no statistically significant difference between metformin and OCP in terms of hirsutism scores, acne scores, BMI, and dysglycaemia.[49] This is in contrast with our meta-analysis where we found that OCP resulted in slightly lower acne scores among girls affected with mild acne and metformin lead in greater BMI reduction, less dysglycemia prevalence, reduced total cholesterol, and reduced LDL. The majority of the adult patients were in the normal BMI range, whereas the majority of the adolescent patients included in our analysis were obese. This may suggest different treatment effects on the basis of baseline BMI.

**TABLE 3** GRADE and Summary of Finding Table

| Quality Assessment | | | | | | | No. of Patients | | Effect | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| No. of Studies | Study Design | Risk of Bias | Inconsistency | Indirectness | Imprecision | Other Considerations | Metformin | OCP | Relative (95% CI) | Absolute (95% CI) | |
| Menstrual cycle regulation (follow-up: mean 6 mo; assessed with number of cycles per month) | | | | | | | | | | | |
| 2 | RCT | Serious[a] | Not serious | Not serious | Serious[b] | None | 22 | 22 | — | MD 0.27 lower (0.33 lower to 0.21 lower) | ⨁⨁◯◯ Low |
| Hirsutism (follow-up: range 6 to 24 mo; assessed with Ferriman Gallwey score) | | | | | | | | | | | |
| 3 | RCT | Very serious[c] | Not serious | Not serious | Serious[c,d] | None | 62 | 65 | — | MD 0.05 higher (0.62 lower to 0.71 higher) | ⨁◯◯◯ Very low |
| BMI (follow-up: range 6 to 24 mo; assessed with kg/m$^2$) | | | | | | | | | | | |
| 4 | RCT | Very serious[c] | Not serious | Not serious | Not serious | None | 72 | 77 | — | MD 4.02 lower (5.23 lower to 2.81 lower) | ⨁⨁◯◯ Low |
| Acne (follow-up: mean 6 mo; assessed with Cook's numeric grading) | | | | | | | | | | | |
| 1 | RCT | Serious[e] | Not serious | Not serious | Serious[f] | None | 16 | 15 | — | MD 0.3 higher (0.05 higher to 0.55 higher) | ⨁⨁◯◯ Low |
| Dysglycemia (follow-up: range 6 to 24 mo; assessed with number of girls with diabetes and prediabetes) | | | | | | | | | | | |
| 2 | RCT | Serious[g] | Not serious | Not serious | Serious[f] | None | 7/38 (18.4%) | 19/43 (44.2%) | RR 0.41 (0.19 to 0.86) | 0 fewer per 1000 (from 62 fewer to 358 fewer) | ⨁⨁◯◯ Low |
| Total testosterone (follow-up: range 6 to 24 mo; assessed with nmol/L) | | | | | | | | | | | |
| 4 | RCT | Very serious[c] | Not serious | Serious[h] | Not serious | None | 72 | 77 | — | MD 1.2 higher (0.91 higher to 1.5 higher) | ⨁◯◯◯ Very low |
| Triglyceride (follow-up: mean 6 mo; assessed with mg/dL) | | | | | | | | | | | |
| 3 | RCT | Very serious[c] | Not serious | Serious[h] | Serious[b,i] | None | 32 | 37 | — | MD 9.69 lower (31.32 lower to 11.95 higher) | ⨁◯◯◯ Very low |
| Total Cholesterol (follow-up: mean 6 mo; assessed with mg/dL) | | | | | | | | | | | |
| 2 | RCT | Very serious[c] | Not serious | Serious[h] | Serious[b] | None | 22 | 25 | — | MD 43.23 lower (64.15 lower to 22.32 lower) | ⨁◯◯◯ Very low |
| LDL (follow-up: mean 6 mo; assessed with mg/dL) | | | | | | | | | | | |
| 2 | RCT | Very serious[c] | Not serious | Serious[h] | Serious[b] | None | 22 | 25 | — | MD 35.5 lower (57.45 lower to 13.55 lower) | ⨁◯◯◯ Very low |
| HDL (follow-up: mean 6 mo; assessed with mg/dL) | | | | | | | | | | | |
| 3 | RCT | Very serious[c] | Not serious | Serious[h] | Serious[b] | None | 32 | 37 | — | MD 2.24 higher (3.83 lower to 8.32 higher) | ⨁◯◯◯ Very low |

Question: Among adolescents aged 11 to 19 y with PCOS, does the use of metformin compared with oral combined contraceptive pill improve menstrual cyclicity, reduce clinical hyperandrogenism, and improve metabolic profile? Setting: outpatients. 0, downgrade of evidence level. MD, mean difference.

[a] One study performed semiopen the concealment of allocation for the metformin group, and had high loss of follow-up.

[b] Not meeting optimal information size criteria.

[c] Two out of 3 studies were high risk of bias (unblinded, no concealment, high loss of follow-up).

[d] CI contains MD = 0.

[e] Unblinded study.

[f] Not meeting optimal information size criteria.

[g] Unblinded study, high loss of follow-up.

[h] Surrogate outcome.

[i] Point estimates and CI were not precise.

Interestingly, the majority of the studies, including adult studies, did not reveal the menstrual cycle frequency for any patient with PCOS started on OCP, possibly on the basis of the assumption that OCP use is associated with regulated menstrual cycles (scheduled bleeding; ie, mean of 1 cycle per month). However, we demonstrated that the difference between metformin and OCP intervention as to how it impacts menstrual cycle regularity is probably clinically not significant (WMD 0.27 per month, equivalent to a difference of 3.24 months per year). This could be related to the definition of menstrual irregularity as most clinicians usually label menstrual cycle pattern abnormality only if the frequency of menses is less than 8 per year.[4] Additionally, menstrual cycle bleeding patterns among healthy women taking OCP over a 12-month period may present with up to a 20% amenorrhea rate (defined as absent menstrual bleed for more than 2 months).[44–47] The observed amenorrhea could be due to poor compliance with OCP intake, reproductive organs immaturity, and other biological causes such as abnormal endometrial function. Abnormal endometrial function is apparent in other ways in PCOS as adult women with PCOS undergoing fertility treatments with proof of ovulatory cycles still express low pregnancy rates and higher spontaneous miscarriages rates, and menopausal women with PCOS are at higher risk for endometrial cancer.[18,50] Therefore, menstrual cycle bleeding patterns while on treatment PCOS provides valuable information about endometrial health and should therefore be closely monitored.

Moreover, our results indicate that metformin use is associated with a lower rate of dysglycemia. The interpretation of this association is challenging. It may be that patients treated with metformin have improvement in glycemic indices or that OCP use is perhaps associated with worsening dysglycemia. Future studies need to reveal incident dysglycemia posttreatment to shed light on this finding.

The strengths of our review include the following: we performed a very sensitive search strategy by using multiple iterations established with the help of a librarian with expertise in systematic reviews. Additionally, we performed a gray literature search through clinical trials registries and conferences proceedings (see Supplemental Information). Additionally, we reported on patient important outcomes with emphases on menstrual cycle regulation. Finally, the choices of included outcomes were based on 3 expert perceptions (2 pediatric endocrinologists and 1 general pediatrician) who helped shed light onto potential patient important outcomes.

There are a number of potential limitations in the review process. We included studies limited to adolescents, and we are now conducting a network meta-analysis of studies that included both adolescent and adult patients with PCOS. To obtain more information to complement incomplete outcome data, we contacted the authors of all included studies. All of them responded. However, some of the outcomes sought after for this review were not available for various reasons.

## CONCLUSIONS

We found that metformin and the OCP had similar results in improvement of hirsutism scores, triglyceride, and HDL levels. OCP was superior for regulating menses regulation and improving acne scores. Metformin was superior for BMI reduction and was associated with a decreased prevalence of dysglycemia and improved total cholesterol and LDL levels. However, these estimates are derived from very low to low quality evidence involving small studies limited to adolescents and as such the true effect may be substantially different from that estimated in this review. Clinicians should be cautious advising for or against metformin or OCP use when treating adolescents with PCOS and need to include patients' values and preferences, as well as potential adverse events in the decision-making process. Future high quality, randomized, concealed, blinded, and well-powered studies are needed to answer several questions for the treatment of adolescents with PCOS in particular relating to impact on hyperandrogenic features, dysglycemia, BMI, and improvement of cardiometabolic outcomes in this patient population.

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## ABBREVIATIONS

CI: confidence interval
GRADE: Grading of Recommendations Assessment, Development, and Evaluation Working Group
HDL: high-density lipoprotein
LDL: low-density lipoprotein
NIH: National Institutes of Health
OCP: oral contraceptive pill
PCOS: polycystic ovarian syndrome
RCT: randomized controlled trial
RR: risk ratio
T2DM: type 2 diabetes mellitus
WMD: weighted mean difference

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